Working Group on Trauma Research Program Summary Report

National Heart Lung Blood Institute (NHLBI), National Institute of General Medical Sciences (NIGMS), and National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH), and the Department of Defense (DOD)

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Trauma is a major public health burden and remains one of the most important priorities for healthcare in the United States, accounting for up to 10% of the entire healthcare budget.[1] The epidemiology and causes of death following trauma are well described.[2–4] These include immediate lethal injuries (the target of prevention), deaths that occur in the first twenty-four hours following injury from bleeding and closed head injury (the target of trauma centers), and deaths that occur greater than 5-7 days following injury from sepsis and multiple organ failure (the target of Surgical Critical Care Units). Despite its magnitude, targeted funding for research and the development of organized clinical trials in trauma has lagged behind other diseases such as cancer and heart disease, delaying advances in care.

The common agenda of injury and its prevention creates many opportunities for collaboration between NIH institutes, other government funding agencies such as the Centers for Disease Control (CDC) and the military, and for increasing the research efforts in trauma. Many basic science and clinical questions remain unanswered due to lack of an organized research infrastructure to address them.

The PULSE (Post-Resuscitative and Initial Utility in Life Saving Efforts) Workshop convened in June 2000 during which specific area-focused work groups were assigned to broadly evaluate resuscitation research and set a vision for future research efforts.[5] An initial trauma work group was formed in 2000 as part of PULSE, and published its findings in 2003.[6]

As a continuation of this effort, the National Heart Lung and Blood Institute (NHLBI) has continued to facilitate PULSE activities, including regular conference calls to further the original goals and objectives. In late 2002 the NHLBI and the Department of Defense called for a combined conference to identify gaps in our current knowledge of the basic science of trauma and to create opportunities for the performance of clinical trials. The PULSE Trauma Program Working Group was convened to provide an interdisciplinary forum on promising and novel life saving therapies in settings of life threatening trauma, and to identify the most promising new directions for trauma resuscitation research. It was organized under a multiagency initiative supported by the National Heart Lung Blood Institute (NHLBI), National Institute of General Medical Sciences (NIGMS), and National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) within the Department of Health and Human Services (DHHS), and the Department of Defense (DOD). The working group was held July 14–15, 2003, at Walter Reed Army Institute of Research in Washington, DC. The primary aim was to identify opportunities for further research as well as areas needing immediate translational research through clinical trials. The key topic areas focused on: 1) cellular injury, 2) bleeding and thrombosis, 3) CNS injury, and 4) multiple organ failure. Within each topic area the working group identified areas that were of greatest priority, and developed a comprehensive and logical set of goals and objectives. The overall program is shown in Table 1.

The NIH roadmap was published in November 2003 and emphasizes NIH priority areas to be: a) building blocks, biological pathways and networks; b) molecular libraries and imaging; c) structural biology; d) bioinformatics and computational biology; and e) nano medicine. Research teams in the future will be interdisciplinary and goal oriented with a focus on reengineering the clinical research enterprise. The following recommendations fit well into this overall roadmap and are consistent with the future of NIH and DoD supported research.[7]

The Working Group Recommendations are divided into four sections: 1) basic science recommendations, 2) potential clinical treatments needing clinical trials evaluation, 3) clinical research opportunities needing attention, and 4) opportunities to facilitate resuscitation research in trauma.

Basic Science Recommendations

1. Study cellular reprogramming in response to trauma and interventions.

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Support for this workshop was provided by the National Heart Lung and Blood Institute, the Department of Defense, the National Institute of Neurological Diseases and Stroke, the National Institute of General Medical Sciences, and the American College of Surgeons Committee on Trauma.

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Table 1 **NIH and DoD Working Group on Trauma Research Program, Walter Reed Army Institute of Research, July 14th–15th, 2003, Washington, DC**

Day 1	
General Session:	
Welcome	Dr. Baraba Alving
Charge to the Group	COL Jeffrey Davies
	Dr. Robert Vandre
	Dr. George Sopko
	Dr. Jim Atkins
Introduction by Chairs	Dr. David Hoyt
	Dr. John Holcomb
	Dr. Edward Abraham
Overview: the trauma patient: cause of death	Dr. David Hoyt
Session 1: Trauma and Mechanisms of Cellular Injury	
Moderator: Dr. David Hoyt	
· Adaptations and genetic variability: responses to cellular hypoxia and ischemia	Dr. Maier
· Cellular activation, apoptosis: responses to ischemia, hemorrhage, and trauma	Dr. Billiar
· Neurotransmitters: acetylcholine and vagal responses in ischemia and injury	Dr. Tracey
· Ischemia/reperfusion and oxidant induced cellular damage	Dr. Rotstein
· Immunomodulatory effects of red cell transfusions, hemoglobin solutions, hyperosmolar solutions and newer crystalloids	Dr. Rhee
· Discussion and Recommendations (Becker, Junger, Tsokos, Pruitt, Fabian, Velmahos)	Panel
Working Lunch: Clinical Studies Concepts and Designs	
Moderators: Drs. Sopko and Marler	
· Discussion and Recommendations (Meredith, Nichol, Pepe)	Panel
Session 2: Endothelial and Coagulopathic Alterations	
Moderator: Dr. John Holcomb	
· New links between the hemostatic and inflammatory systems that are relevant to trauma and its complications	Dr. Zimmerman
· Coagulation and organ dysfunction: responses to trauma, cellular ischemia and hemorrhage	Dr. Aird
· Hemostasis interventions: following disseminated intravascular coagulation or pathophysiological states—hypothermia, acidosis, and massive blood loss	Dr. Hess
· Strategic targets for coagulation and endothelial alterations following blood loss and injury	Dr. Holcomb
· Discussion and Recommendations (Moore, Lawson, Scalea, Tompkins, Cairns)	Panel
Session 3: Cerebral Protection and Neurologic Preservation	
Moderator: Dr. Claudia Robertson	
· Cerebral microcirculation: responses to trauma, hypoxia and hypotension	Dr. Iadecola
· Cerebral protection: promising pharmacotherapy for ischemia and neurological injury	Dr. Bullock
· Cerebral and neurologic function: role of induced hypothermia for ischemia and neurologic injury	Dr. Ginsberg
· Cerebral preservation following injury: clinical outcomes and assessment	Dr. Hannay
· Discussion and recommendations (Ling, Mattox, Valadka, Clark, Jurkovich)	Panel
Individual Breakout Groups Sessions	Chairman, Moderator and Panel Members Only
Draft Report Write Ups	
Day 2	
Session 4: Lung & Other Organ Injury Following Shock & Trauma	
Moderator: Dr. Edward Abraham	
· Mechanisms of acute lung injury after hemorrhage and trauma	Dr. Abraham
· Interactions between liver, intestine, and lung after hemorrhage and trauma	Dr. Fink
· Mechanisms of ventilator induced lung injury and their implications in early resuscitation of blood loss and trauma	Dr. Slutsky
· Mechanisms of renal injury after trauma and blood loss	Dr. Mehta
· Discussion and Recommendations (Champion, Coimbra, Jones, Tisherman, Hirschl, McSwain, Hirsch)	Panel
Individual Breakout Groups Sessions	Chairman, Moderator and Panel Members Only
Draft recommendations	
Session Recommendations: Panel Discussion	Session 1–4 Moderators
Summary Statement	Drs. Abraham, Hoyt, Holcomb
Closing Remarks	Drs. Atkins, Somers, Michel
Draft Report and Final Writing Assignments	Working Group Chairs

2. Study the immune response following injury (including regulation by neuroendocrine factors, coagulation, inflammation, and treatment effects).
3. Create an animal consortium to create animal models of injuries, specifically to include multiple trauma models with and without brain injury and allowing evaluation of the *timing* of interventions. This should include mouse models to allow evaluation of genetic effects.
4. Profile patient and animal models following injury for genomics, proteonomics, as well as other biomarkers.
5. Develop biochemical, physiologic, and clinical phenotypic states following injury based on data collected through animal and clinical studies.

Cellular Reprogramming

It is clear from multiple studies that reprogramming of the cellular response and intracellular signaling occurs following trauma and following therapeutic interventions. Examples include: changes in gene expression, changes due to alteration of the cytokine response, and changes due to oxidative stress, to name just a few. Fundamental to the development of therapeutic strategies to treat the injured patient is a better understanding of the pathophysiology of cellular reprogramming that accompanies trauma and subsequent interventions.

Fundamental Studies on the Immune Response

The immune response following injury and shock is critical to either the subsequent development of host resistance to infection or the development of multiple organ failure. The effects of neuroendocrine factors, coagulation factors, other inflammatory systems, and the effects of treatment need to be studied in great detail in order to target and assess potential therapies prior to animal testing and clinical trials. The ability to manipulate the immune response following injury is essential to improving postinjury therapy, and intensive studies targeted to better understand the immune response are critical.

Creation of Animal Models

Consistent ways to study trauma in animal models are lacking due to disagreement as to which models are most representative, inconsistent methodology among models studied, and between-center differences in animal models. The critical needs include: a) development of an animal consortium with standardized models and methodologies to allow reproducibility and comparability across centers, and b) develop specific models to allow assessment of multiple trauma, the presence of multiple trauma with and without brain injury, and chronic models that will allow assessment of interventions aimed particularly toward cellular reprogramming and the immune response. This also includes the development of mouse models to allow evaluation of genetic effects of injury by using genetically different murine strains now widely available.

Patient and Animal Model Genomic Profiling

To better understand the *in vivo* response following injury, genomic expression and proteonomic expression need to be studied longitudinally in order to profile chronic animal models and patients over time. Changes in genomics and proteonomics, as well as other biomarkers, through organized multicenter data collection and consistent measurement of these responses are essential to understand the basic cellular physiologic response following injury over time. Translational research of cellular reprogramming and immune responses requires a better understanding of the *in vivo* response to design timing and targeting of clinical interventions.

Develop Phenotypic States

It is believed that the complexity of the postinjury response ultimately will be better described by profiling biochemical, cellular, physiologic, and clinical data into several easily identified phenotypic clinical states. This will allow classification and optimal targeting of both patients and therapeutic interventions. The use of data collected in both standardized animal models and standardized clinical assessments within a clinical consortium would create a platform for developing a consensus regarding clinically relevant phenotypic states. This is essential for designing targeted therapeutic intervention as part of organized prospective clinical trials.

Clinical Trials Recommendations

Five areas were identified as opportunities for immediate clinical trials, based on adequate preliminary data. These include:

1. Airway and ventilation strategies.
2. Fluid treatments.
3. Systemic and local hemostatic therapy.
4. Antioxidant therapy and other pharmacologic or metabolic adjuvant therapy.
5. Body temperature modulation.

Airway and Ventilation Strategies

Multiple recent studies have suggested that airway control in the field, though intuitively beneficial, instead may be associated with increased mortality. Specific techniques for ventilation also have been associated with poor outcome in animal models. Before further introduction of routine field airway management continues to be developed, well-controlled multicenter trials should study the efficacy and safety of drug-assisted intubation and examine which ventilation strategies are best for field use. Appropriate monitoring techniques to assure safety need to be developed and studied, as these therapies are introduced, to assure efficacy and safety.

Fluid Treatments

Multiple recent studies have called for reevaluation of whether or not fluid resuscitation is needed, what the ideal fluid resuscitation strategy should be, and whether these are

different depending on transport time to definitive care. Several studies have suggested the need to evaluate fluids such as hypertonic saline solution, hemoglobin solutions, or newer fluids such as ethyl pyruvate in their capacity to provide better oxygenation or avoid excessive inflammatory stimulation following ischemia, reperfusion and shock. Improving the postinjury inflammatory response by attenuating it immediately following injury potentially can allow subsequent avoidance of multiple organ failure. Testing of such strategies requires well designed trials that maintain control of prehospital care and outcomes following delivery to trauma centers. The infrequency of specific patients in a single center will require multicenter trials in order to assess these questions effectively.

Systemic and Local Hemostatic Therapy

The availability of systemic adjuvants for enhancing coagulation and the availability of new local hemostatic therapy present an exciting opportunity to control bleeding and potentially avoid bleeding related complications. One of the most challenging situations includes increased intracranial pressure in head injury or significant complications following major bleeding in torso and extremity trauma. Clinical trials to evaluate therapies such as Factor VIIa or topical hemostatic dressings in torso trauma and extremity injuries need to be conducted in a variety of settings including the field, emergency department, and operating room.

Antioxidant Therapy and Other Pharmacologic and Metabolic Adjuvant Therapy

There are currently several adjuvants that might beneficially affect the postinjury immune responses and fundamental aspects of cellular reprogramming that lead to multiple organ failure. Therapeutic trials should be designed to evaluate such therapies. Examples of such trials include the use of antioxidant therapy or complement inhibitors to attenuate the postinjury inflammatory response.

Body Temperature Modulation

A body of data suggest that the use of hypothermia as an adjuvant resuscitative measure both following shock and following head injury may have value. Well designed clinical studies that evaluate this as potential field therapy, therapy in the emergency department, or as an adjunct to therapy in the operating room or intensive care unit (ICU) should be done.

Clinical Research Opportunities

1. Development of biosensors for all aspects of care including prehospital, emergency department, operating room, and ICU monitoring. These should include cardiovascular, coagulation and inflammatory, metabolic, and neurologic monitoring capabilities.
2. Development of computational abilities to deal with large volume data analysis from complex longitudinal studies of both animal models and clinical data.
3. Implementation of automated data acquisition, whenever feasible, to assure uniformity of data collection; and to facilitate collection of critical information, such as EMT response time, travel times to the Level 1 Trauma Center, and time to surgical intervention.

Biosensors

The need to improve the ability to monitor the physiologic responses of the cardiovascular system, the inflammatory and coagulation system, metabolic responses, and neurologic responses is critical to identify patients at risk for clinical deterioration and to better understand the relevance of basic science observations in subcellular physiologic and animal models.

Ultimately, the ability to describe clinical phenotypic states that identify patients at risk, patients needing therapeutic intervention, and their response to therapeutic intervention will be essential to achieve better clinical outcomes. There is a need to develop biosensors that can be used in hostile environments and have radiotelemetry capability, measure subcellular phenomena, and integrate and process signals into physiologic states. Opportunities to pursue these efforts in conjunction with the biotechnology industry should be pursued.

Computational Capability

The high volumes of data that need to be collected in the studies to profile animal and clinical phenotypic states and better understand specific cellular reprogramming and responses of the immune and coagulation system require sophisticated computational capabilities. This will allow analysis of large volumes of data within isolated single *in vitro* experiments as well as analysis of complex longitudinal studies of both animal and clinical data. Development of computational cores and standardized methods and procedures is essential to the ability to explore these questions.

Specific Opportunities to Facilitate Trauma Resuscitation Research

1. Develop an informed consent process that is consistent and comprehensive to address local Institutional Review Board (IRB) issues.
2. Develop a preclinical animal model consortium to develop and test treatments targeted for clinical applications.
3. Establish a clinical consortium to initiate and maintain infrastructure to conduct appropriate clinical studies and multicenter trials to rapidly translate promising strategies.
4. Develop centralized tissue banks for collection of large volumes of tissue and core analytical laboratories to achieve consistent and standardized specimen management.
5. Develop standardized computational centers to assist with data handling and statistical analysis.

Informed Consent Process

Prehospital research and research in the emergency environment always have been limited by the inability to obtain individual informed consent due to the nature of the patient's disease. In addition, there is a site specific variability among IRB processes within an area or across the country, leading to inconsistent interpretation of protocols and confounds the ability to perform multicenter research. Many questions will not be answered unless these barriers to facilitate and conduct multicenter trials can be overcome. The development of a uniform process for informed consent and the ability to work with local IRBs to get standardized procedures for this kind of research is essential. Organizational procedures and the development of standardized rules sensitive to this need will help with this effort.

Preclinical Animal Model Consortium

The development of new strategies requires multi-disciplinary approaches, testing, and validation of standardized models in small animals and large animals and across the laboratories to facilitate the translation of appropriate treatments into clinical trials. Establishment of a preclinical (animal model) multi-laboratory consortium will fast track therapies and other promising results that emerge out of basic science recommendations.

Clinical Consortium

Testing of promising strategies and hypotheses regarding treatment of the injured patient requires the identification of appropriate patient populations and the ability to recruit adequate numbers of patients. The nature of the variability in outcome and the need to study the most severely injured patients to test these therapies will necessitate using more than a single center. Organized trauma centers, which exist throughout the country, offer a unique opportunity for multiple studies to be conducted simultaneously. Without a well funded clinical consortium, it is unlikely that many of these promising strategies could be studied effectively.

Development of a clinical consortium guided by the experience gained within the NIH assures that relevant questions are asked, appropriate trials are designed, appropriate outcomes are assessed, and appropriate conclusions are reached. Such consortiums also allow for independent hypothesis testing or collaboration with industry to conduct relevant trials, and provides a unique environment for training of new clinical researchers. Oversight by the NIH adds credibility to the results by maintaining the independence of the investigation and managing of conflict of interest.

Centralized Tissue Banks

Development of centralized tissue banks for the collection of large volumes of tissue and blood samples should be done, establishing core laboratories to achieve standardized, high quality and consistent results. The creation of an award program to encourage centralized tissue and blood sample banks as well as laboratories that will perform large volume sample analysis will improve overall research in both clinical and animal research activities.

Statistical and Computational Support

Facilitation of resuscitation research should be supported by the best models for computational needs and by use of appropriate statistical design. The development of centers of excellence for this type of support is essential for the clinical and animal consortia.

SUMMARY

The opportunities for advancing research in trauma are multiple and outstanding. The Working Group on Trauma Research Program identified frontiers for both basic science study and clinical research opportunities, with priorities for study in clinical trials, to advance resuscitation research overall. These recommendations are relevant, realistic, and with appropriate multi-institutional support will create a robust agenda for improving the care of the injured patient in both civilian practice and in the battlefield.

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